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Myasthenic Crisis

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Abstract

Myasthenic crisis is a complication of myasthenia gravis characterized by worsening of muscle weakness, resulting in respiratory failure that requires intubation and mechanical ventilation. Advances in critical care have improved the mortality rate associated with myasthenic crisis. This article reviews the epidemiology of myasthenic crisis and discusses patient evaluation. Therapeutic options including mechanical ventilation and pharmacological and surgical treatments are also discussed.

Keywords

myasthenia gravis, autoimmune diseases of the nervous system, neurocritical care clinical specialty, neuromuscular disease clinical specialty

Myasthenia gravis (MG) is an autoimmune disorder affecting neuromuscular transmission, leading to generalized or localized weakness characterized by fatigability.[1] It is the most common disorder of the neuromuscular junction, with an annual incidence of 0.25-2 patients per 100 000.[2] Myasthenia gravis is most frequently associated with antibodies against acetylcholine receptors (AChR) in the post-synaptic motor end plate.[3] A second form of myasthenia gravis, usually seen in young women, involves antibodies against muscle-specific tyrosine kinase (MuSK).[4] A third group of patients has antibodies to neither AChR nor MuSK, and these patients are considered seronegative. Clinically, these patients are similar to patients with AChR antibodies.[3] Myasthenic crisis is a complication of MG characterized by worsening muscle weakness, resulting in respiratory failure that requires intubation and mechanical ventilation.[1] A more comprehensive definition of myasthenic crisis also includes post-surgical patients, in whom exacerbation of muscle weakness from MG causes a delay in extubation.[5]

Epidemiology

Fifteen to 20% of myasthenic patients are affected by myasthenic crisis at least once in their lives.[1] The median time to first myasthenic crisis from onset of MG ranges from 8-12 months.[6,7] However, myasthenic crisis may be the initial presentation of MG in one-fifth of patients.[7,8] Overall, women are twice as likely as men to be affected. A bimodal distribution of myasthenic crisis is seen. An early peak prior to age 55 affects women 4:1, whereas a later peak after age 55 affects women and men equally.[6] The average age of admission with myasthenic crisis is almost 59 years. Patients in crisis requiring endotracheal intubation spend a median of 17 days in the hospital. Eighteen percent of patients admitted with myasthenic crisis will require discharge to a rehabilitation center.[9]

Advances in mechanical ventilation and critical care have been paramount in improving mortality associated with myasthenic crisis. During the early 1960s, respiratory care of these patients was transitioned from negative external pressure ventilation to positive pressure ventilation in an intensive care unit. The mortality rate from myasthenic crisis declined from 42% in the early 1960s to 6% by the late 1970s, and the median age at death increased.[10] Currently, mortality is 4% and is primarily the result of comorbid medical conditions.[6]

Assessment of Respiratory Dysfunction in Myasthenic Crisis

Myasthenic crisis can involve the upper airway muscles, respiratory muscles, or a combination of both muscle groups.[11] Both inspiratory and expiratory respiratory muscles can be affected, manifesting as dyspnea.[12] Inspiration is performed primarily by the diaphragm and external intercostal muscles and secondarily by the sternocleidomastoid and scalene muscles. Although expiration is primarily passive, the abdominal and internal intercostal muscles can be recruited to assist.[11] In MG with AChR antibodies, muscle weakness

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tends to initially affect the intercostal and accessory muscles and then the diaphragm.[3]

Inspiratory function is measured by both vital capacity (VC) and negative inspiratory force (NIF); expiratory function is measured by positive expiratory force (PEF).[11] A VC less than 1 L (or <20-25 mL/kg) or an NIF <20 cm H2O indicates significant respiratory weakness; both measurements are commonly used to define myasthenic crisis.[13,14] In addition, a PEF <40 cm H2O may indicate crisis.[15] Regardless of respiratory function indices, the need for mechanical ventilation is a sufficient criterion to define myasthenic crisis.[13]

Inspiratory and expiratory forces are more sensitive than VC in evaluating muscle strength in MG.[12] In a retrospective review, repeated measurement of VC did not predict the need for intubation and mechanical ventilation in myasthenic crisis.[16] Facial weakness can lead to inaccurate measurements of all 3 indices.[15] At the bedside, recruitment of accessory muscles indicates significant inspiratory muscle weakness, and a weak cough or difficulty counting to 20 in a single breath signifies weakness of the expiratory muscles.[11]

Respiratory dysfunction also manifests as upper airway obstruction if weakness of the upper airway or bulbar muscles is present.[17] Myasthenic patients with MuSK antibodies preferentially exhibit bulbar weakness before respiratory muscle weakness.[3] Upper airway weakness can lead to respiratory failure by oropharyngeal collapse or tongue obstruction and by increasing the work of already fatigued respiratory muscles against a closed airway.[17] Signs of bulbar weakness include dysphagia, nasal regurgitation, a nasal quality to speech, staccato speech, jaw weakness (jaw closure weaker than jaw opening), bifacial paresis, and tongue weakness.[14]

Respiratory Management of Myasthenic Crisis

Intubation and Mechanical Ventilation

Respiratory support is imperative in the management of myasthenic crisis. Two-thirds to 90% of patients with myasthenic crisis require intubation and mechanical ventilation.[6,8] Over 20% of patients require intubation during evaluation in the emergency department, and almost 60% are intubated after admission to an intensive care unit.[6] Elective intubation of a myasthenic patient with impending respiratory failure is favored over emergent intubation. Once intubated, patients should be placed on an assisted ventilator setting with tidal volumes of 8-10 cc/kg ideal body weight and pressure support of 8-15 cm H_2O to prevent atelectasis and to minimize the work of breathing. The degree of support required is ultimately patient dependent.[18]

Neuromuscular blocking agents (paralytics) should be used with caution when intubating MG patients. Depolarizing agents (for example, succinylcholine) are less potent in myasthenics because fewer functional post-synaptic AChR are available. This decrease in receptors also results in a decrease in the safety margin or remaining AChR available for neuromuscular transmission. Nondepolarizing agents (for example, vecuronium) have increased potency, and reduced doses are required for paralysis.[19]

Weaning from the ventilator should be initiated after the patient demonstrates clinical improvement, typically at a vital capacity of more than 15 mL/kg.[18,20] Improvement in the strength of neck flexors and other adjunct muscles usually is associated with improvement in bulbar and respiratory muscle strength and can be a useful tool for assessing clinical improvement.[20] Patients should be transitioned to a spontaneous mode of ventilation (eg, pressure support ventilation) in which all breaths are patient initiated. Pressure support can then gradually be decreased to minimal settings. If the patient does not tolerate weaning, an assisted ventilator setting should be reinstituted.[18]

It remains unclear when first to attempt extubation after myasthenic crisis. Only half of patients are extubated at 13 days.[6] In 1 series, 3 independent risk factors for prolonged intubation (>14 days) were identified: age >50 years, peak vital capacity <25 mL/kg on post-intubation days 1 to 6, and a serum bicarbonate ≥30 mmol/L. All of the patients with no risk factors were intubated for less than 2 weeks, whereas 88% of the patients with all 3 risk factors had prolonged intubation. Patients with a prolonged intubation were hospitalized 3 times longer and were less likely to be functionally independent upon discharge.[6] Thymoma is also associated with a worse prognosis in myasthenic crisis.[8]

Fluctuating weakness and pulmonary complications often confound the decision to extubate.[21] A maximal expiratory pressure has been demonstrated to independently predict extubation success. Extubation failure is most commonly associated with a weak cough and inadequate airway clearance.[22] Older age, atelectasis, and pneumonia are also associated with extubation failure.[7] Tracheostomy placement ranges from 14%-40%.[6,7]

Reintubation occurs more than one-fourth of the time.[7,21] Acidosis, decreased forced vital capacity (FVC), atelectasis, and need for noninvasive ventilatory support are predictors of reintubation.[21] Two retrospective studies found atelectasis in all patients requiring reintubation.[7,21] To prevent atelectasis, early intubation, aggressive chest physiotherapy, and frequent suctioning should be implemented and high positive end-expiratory pressure given while the patient is mechanically ventilated.[23] Reintubaton is a significant event because patients requiring reintubation have significantly longer ICU and hospital stays.[7]

Noninvasive Ventilation

Noninvasive ventilation (NIV) may be used to prevent intubation or reintubation of patients in myasthenic crisis.[22] With bilevel positive airway pressure (BiPAP), positive pressure is applied during both phases of respiration, enhancing airflow and alleviating the work of breathing during inspiration and

Table 1. Precipitants of Myasthenic Crisis

Stressors	Medications
Physical stressors	α-Interferon
Aspiration pneumonitis	Antibiotics
Infection	Aminoglycosides
Perimenstrual state	Gentamicin
Pregnancy	Streptomycin
Sleep deprivation	Ampicillin
Surgery	Macrolides
Environmental Stressors	Erythromycin
Emotional stress	Quinolones
Pain	Ciprofloxacin
Temperature extremes	Polymyxin
Tapering of immune-modulating medications	Antiepileptics
	Gabapentin
	Phenytoin
	β-Adrenergic antagonists
	Calcium channel antagonists
	Contrast media
	Magnesium
	Methimazole
	Prednisone
	Procainamide
	Quinidine

Table 2. Symptoms of Cholinergic Crisis

Nicotinic toxicity
Muscle weakness
Fasciculations
Muscarinic toxicity
Diaphoresis
Excessive tearing
Increased oral and pulmonary secretions
Nausea and vomiting
Diarrhea
Bradycardia

preventing airway collapse and atelectasis during expiration.[24] One retrospective study found that 20% of patients in myasthenic crisis could be successfully supported with NIV. In patients who are initially managed with NIV, endotracheal intubation and mechanical ventilation should be initiated if the patient has continued or worsening shortness of breath, increased work of breathing, tachypnea, or hypercapnea. Independent predictors of NIV success are a serum bicarbonate <30 mmol/L and an APACHE II score <6.[22] An independent predictor of NIV failure is hypercapnia (PCO2 >45mm Hg).[24] Vital capacity, NIF, and PEF are not useful in predicting outcome.[25]

Initial use of NIV is associated with a shorter duration of ventilatory support. Patients treated initially with NIV require ventilatory support for a median of 4 days versus 9 days in those patients initially intubated. In addition, these patients spend one-third less time in the ICU and in the hospital.[24] In 2 studies, NIV prevented reintubation in 70% of patients.[22,25] In patients with bulbar weakness, NIV might increase the risk of aspiration.[22] However, 1 retrospective cohort study found no difference in pulmonary complications between those supported with NIV and those supported with endotracheal intubation mechanical ventilation. In patients successfully supported with NIV, there were significantly fewer pulmonary complications.[24]

Complications in the Management of Myasthenic Crisis

Fever is the most common complication associated with myasthenic crisis. Infectious complications include pneumonia, bronchitis, urinary tract infections, *Clostridium difficile* colitis, bacteremia, and sepsis.[6] When compared to patients admitted for non-crisis MG, patients admitted with myasthenic crisis are more likely to experience sepsis, deep vein thrombosis, and cardiac complications including congestive heart failure, acute myocardial infarction, arrhythmias, and cardiac arrest. These complications, however, are not independent predictors of mortality.[9] In 1 series, atelectasis, *C. difficile* colitis, transfusion-dependent anemia, and congestive heart failure were independently associated with a longer duration of myasthenic crisis, but not with a longer duration of intubation.[6]

Precipitants of Myasthenic Crisis

Common precipitants of myasthenic crisis are shown in Table 1. The most common precipitant is infection.[6,8] One series documented infection in 38% of patients presenting with myasthenic crisis; most commonly, the infection was bacterial pneumonia followed by a bacterial or viral upper respiratory infection.[6] Other precipitants include aspiration pneumonitis, surgery, pregnancy, perimenstrual state, certain medications (see below), and tapering of immune-modulating medications.[6,8,11] Other antecedent factors include exposure to temperature extremes, pain, sleep deprivation, and physical or emotional stress.[26] Approximately one-third to one-half of patients may have no obvious cause for their myasthenic crisis.[6,8]

Numerous medications may exacerbate MG, including quinidine,[27] procainamide,[28] β-adrenergic antagonists,[29] calcium channel antagonists (verapamil, nifedipine, felodipine),[30-32] magnesium,[33] antibiotics (ampicillin, gentamicin, streptomycin, polymyxin, ciprofloxacin, erythromycin),[34-38] phenytoin,[39] gabapentin,[40] methimazole,[41] α-interferon,[42] and contrast media.[43] These medications should be used cautiously in myasthenic patients, especially after surgery. Any medication suspected of precipitating myasthenic crisis should be discontinued.[26]

Although corticosteroids can be used in the treatment of MG, initial treatment with prednisone led to an exacerbation of MG in almost half of patients in 1 series.[44] The incidence of myasthenic crisis resulting from corticosteroids ranges from 9%-18%.[44,45] Thus, commencement of corticosteroids for the treatment of MG should always occur in a hospital

Table 3. Comparison of Intravenous Immunoglobulin to Plasma Exchange

	IVIg	PE
Dose	400 mg/kg × 5 d	One plasma exchange every other day over 10 d
Response	Improvement in 4-5 d; effect for 4-8 wk	Improvement in 2 d; effect for 3-4 wk
Advantages	More readily available	Faster treatment response
Disadvantages	Slower treatment response	Need for special venous access, equipment, and personnel
Contraindications	IgA deficiency	Hemodynamic instability, unstable coronary disease, current internal bleeding
Serious complications	Aseptic meningitis, cardiac arrhythmia, thrombocytopenia, thrombotic events	Hemodynamic instability, cardiac arrhythmia, myocardial infarction, hemolysis

Abbreviations: IVIg, intravenous immunoglobulin; PE, plasma exchange.

setting, where respiratory function can be monitored.[44] Predictors of exacerbation from prednisone include older age, lower score on the Myasthenia Severity Scale (a clinical assessment tool), and bulbar symptoms.[45]

Cholinergic Crisis

Patients taking an excess of acetylcholinesterase inhibitors may precipitate a cholinergic crisis characterized by both muscarinic and nicotinic toxicity (Table 2).[15] Symptoms may include an increase in perspiration, lacrimation, salivation and pulmonary secretions, nausea, vomiting, diarrhea, bradycardia, and fasciculations.[11,15] Although cholinergic crisis is an important consideration in the evaluation of the patient in myasthenic crisis, it is uncommon.[15] One retrospective series of patients with myasthenic crisis found none of the patients had cholinergic crisis.[6] Regardless of whether myasthenic or cholinergic crisis is suspected, acetylcholinesterase inhibitors should be significantly lowered or discontinued to avoid excessive pulmonary secretions in the setting of respiratory distress.[11]

Treatment of Myasthenic Crisis

The 2 primary pharmacologic therapies available for myasthenic crisis are intravenous immunoglobulin (IVIg) and plasma exchange (PE) (Table 3). A typical course of IVIg is 400 mg/kg daily for 5 days.[13] Patients should be screened for IgA deficiency to avoid anaphylaxis from IVIg.[46] The most common side effect associated with IVIg is headache. Other complications include fever, nausea, IV site discomfort, rash, malaise, aches and pain. More serious adverse events can include aseptic meningitis, hypertension, cardiac arrhythmia, thrombocytopenia, and thrombotic events, including stroke, myocardial infarction, and pulmonary embolism.[47,48] For PE, 5 exchanges (1 plasma volume or 3-4 L per exchange) are usually performed every other day over 10 days.[13,49] Replacement fluid is generally a solution of normal saline/5% albumin. Venous access is obtained via large-bore peripheral catheters, or temporary or tunneled double-lumen central venous catheters. Infection and bleeding from obtaining central venous access occurs in less than 2%.[49] Common complications from PE include fever, symptoms from hypocalcemia (primarily paresthesias), a transient decrease in blood pressure, and tachycardia.[49,50] Other more serious, but less common, adverse effects include cardiac arrhythmia, myocardial infarction, and hemolysis.[50] Response to treatment generally occurs after 2 days with PE and after 4-5 days with IVIg.[51] For both treatments, an effect can be seen for several weeks.[20] If there is insufficient or no response to treatment, PE can be given after IVIg, and IVIg can be administered after PE.[46,52] Although there is a theoretical concern that sequential use of PE after IVIg might result in removal of the IVIg, removal is usually done when there has been insufficient response to IVIg, and removal of IVIg is therefore of little concern.

Some evidence exists that PE may be more effective than IVIg in the treatment of myasthenic crisis. A retrospective multicenter study including only patients experiencing myasthenic crisis compared the use of 5 or 6 cycles of PE completed every other day to 400 mg/kg/day of IVIg given for 5 days and found PE to be more effective. Patients who initially received PE had more clinical improvement at 1 week, better respiratory status at 2 weeks, and better functional outcome at 1 month. However, an increased number of complications, mostly infection and cardiovascular instability, were seen in the PE group.[53] Conversely, another study prospectively randomized patients with an exacerbation of MG to 3 cycles of PE or to IVIg 400 mg/kg/day given for 3 or 5 days and found no difference. However, this study was not limited to patients in myasthenic crisis.[54] Overall, one-fifth of patients required a second treatment with either PE or IVIg. Patients who received IVIg as initial treatment more frequently required a second treatment, primarily owing to an absence of early response.[53] In a case series of 4 patients in myasthenic crisis who had failed IVIg, all improved after PE was implemented.[52]

Corticosteroids are used in conjunction with IVIg and PE. High-dose prednisone (60-100 mg daily or 1-1.5 mg/kg/d) may be initiated concurrently with IVIg or PE, since prednisone begins to work after 2 weeks, at which point the effects of PE and IVIg are waning. Enteral administration of corticosteroids is preferred, and initiation of prednisione may be deferred until after the patient is extubated if the patient is

rapidly improving with IVIg or PE treatment.[15] Initial worsening from high-dose prednisone is treated with continued ventilatory support.[26] The mean time to improvement with prednisone in 1 series of patients with MG exacerbation was 13 days. Eighty-five percent of patients showed improvement within 3 weeks. Worsening of symptoms with the initiation of corticosteroids is not predictive of overall response to corticosteroids.[44] Once the patient has begun to show improvement, the prednisone dose can be decreased and gradually converted to alternate-day dosing.[26] The most common side effects from prednisone are a Cushingoid appearance, cataracts, and weight gain.[44] Infection, poorly controlled diabetes, and severe osteoporosis are relative contraindications to instituting corticosteroids.[15]

Cyclosporine may be considered after initiation of IVIg or PE in patients who cannot tolerate or who are refractory to corticosteroids. However, the onset of action of cyclosporine is 1-2 months. Other immunomodulating agents, azathioprine and mycophenolate, are not useful in myasthenic crisis because of their long latency of action.[15]

Abnormal laboratory values that could affect muscle strength should also be corrected. Potassium, magnesium, and phosphate depletion can all exacerbate myasthenic crisis and should be repleted. Hematocrit less than 30% might affect weakness by decreasing oxygen-carrying capacity.[13,18] Adequate nutrition is important to avoid a negative energy balance and worsening of muscle strength.[18]

As mentioned previously, acetylcholinesterase inhibitors are usually discontinued in myasthenic crisis to avoid excessive bronchial secretions.[11] Additionally, continued use of these medications confounds the assessment of other treatment modalities and can increase muscle weakness if used in excess.[13] These medications do not alter the course of the crisis and offer solely symptomatic relief of MG.[11] After patients have shown definitive improvement in muscle strength (usually several days after the initiation of IVIg or PE), acetylcholinesterase inhibitors, typically oral pyridostigmine, may be reinitiated after or just prior to extubation.[11,13] Oral pyridostigmine is preferred, but it may be given intravenously. One milligram of intravenous pyridsotigmine is equal to 30 mg of oral pyridostigmine. Patients should be started on a low dose of the medication that is titrated to symptomatic relief.[13] Continuous intravenous infusion of pyridostigmine as treatment for myasthenic crisis may have efficacy similar to that of plasma exchange, but it is associated with an increased risk of life-threatening cardiac arrhythmia that warrants further study.[55,56]

Thymectomy

Thymic hyperplasia is common in young myasthenic patients with positive AChR antibodies, especially women. Thymic tumors, found in 15% of patients with MG and in 32% of patients with myasthenic crisis, should be treated with thymectomy.[3,6] Patients with non-thymomatous MG can consider thymectomy to improve the likelihood of improvement or remission of the disease.[57] One retrospective study found that myasthenic patients who had undergone thymectomy had fewer incidences of myasthenic crisis and less-severe episodes.[58] A multicenter, single-blind, randomized controlled trial is currently investigating the benefit of thymectomy in non-thymomatous MG.[59]

Postoperative myasthenic crisis is common after thymectomy; the incidence ranges from 12% to 34%.[60,61] Postoperative crisis in these patients has been related to a history of myasthenic crisis, preoperative presence of bulbar weakness, preoperative serum AChR antibody levels >100 nmol/L, and intraoperative blood loss of >1 L.[61]

Conclusions

Myasthenic crisis is a common complication of MG. The advent of positive pressure ventilation in the 1960s has decreased mortality and remains the cornerstone of management. The majority of patients with myasthenic crisis require endotracheal intubation and mechanical ventilation. A select group of patients might benefit from NIV to avoid initial intubation or reintubation.

Factors precipitating myasthenic crisis should be quickly identified and promptly mitigated; half of these patients have no identifiable precipitant. Typically, anticholinesterase inhibitors are discontinued to avoid excessive secretions while the patient is experiencing respiratory failure. Both PE and IVIg, in conjunction with prednisone, may be used to treat myasthenic crisis. Limited data suggest that PE may be more effective than IVIg. Thymectomy remains part of treatment in patients with thymic tumors, but the role of surgery in non-thymomatous MG requires further investigation.

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